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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/818,237	03/27/2001	Larry Gold	NEX 34C-US-D	3250

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Swanson & Bratschun, L.L.C.
Suite 330
1745 Shea Center Drive
Highlands Ranch, CO 80129

EXAMINER	
ZITOMER, STEPHANIE W	
ART UNIT	**PAPER NUMBER**
1634	#12

DATE MAILED: 04/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/818,237	Applicant(s) GOLD ET AL.	
	Examiner Stephanie Zitomer	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34 and 54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Information Disclosure Statement

1. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited on the 1449 or on form PTO-892, they have not been considered.

Informalities: Priority information

2. The disclosure is objected to because of the following informalities:

(a) The priority information in the first paragraph of the specification requires updating as to US patent numbers and WO publication numbers.

(b) The citation to Green et al. at page 78, line 12 is incomplete.

Appropriate correction is required.

Rejection under 35 U.S.C. 112, first paragraph: Inadequate written description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 34 and 56 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to methods of "identifying modified single-stranded ribonucleic acid ligands to PDGF and hKGF" from a candidate mixture of modified RNA. The claimed methods thus encompass a large genus of RNA "modifications" to PDGF and hKGF ligands for which a representative number of species must be described to satisfy the written description requirement and show that applicant was in possession of the full scope of the "modifications" genus at the time the application was filed. The specification makes the general statement at page 27 that the invention encompasses ligands having chemical modifications made to increase *in vivo*

stability or to enhance delivery wherein such modifications include "chemical substitutions at the sugar and/or phosphate and/or base" of a given nucleotide. Methods for identifying different types of modified nucleic acid ligands from modified candidate mixture nucleic acids are described including identifying RNA ligands of TGFβ1 (page 32), PDGF (page 62) and hKGF ligands (page 67) comprising 2'-amino or 2'-fluoro modified deoxypyrimidines. The method is also described for identifying modified DNA ligands to PDGF comprising 5'-iodo-2'-deoxyuridine substitution for thymidine (page 47). Truncation of ligands for determination of affinity boundaries which is a post-SELEX study technique is described at pages 51-58. A single RNA ligand to bFGF, NX-286, was modified with phosphorothioate internucleotide linkages, 2'-deoxy-2'aminopyrimidines, 2'-deoxy-2'-O-methylpurines and phosphorothioate caps (page 78). It is not stated whether a modified ligand was identified using the claimed invention SELEX method. Furthermore, there is no teaching of the applicability of the latter modifications to the claimed invention methods. Thus, according to the disclosure, the description of methods for identifying modified RNA ligands to PDGF and hKGF is limited to performance with a candidate mixture of 2'-deoxy-2'-fluoropyrimidine modified RNA for PDGF in claim 34 and with a candidate mixture of 2'-deoxy-2'aminopyrimidine modified RNA or a candidate mixture of 2'-deoxy-2'-fluoropyrimidine modified RNA for hKGF in claim 56. In addition to enablement the first paragraph of 112 requires a "written description". As set forth by the Court in *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, the written description must convey to one of skill in the art "with reasonable clarity" that as of the filing date applicant was in possession of the claimed invention. For the reasons stated above, the specification fails to convey to the skilled practitioner in the art that applicant was in possession at the time the application was filed of the large genus of modified RNA ligands to PDGF and hKGF encompassed by the claims.

Rejection under 35 U.S.C. 112, second paragraph: Indefiniteness

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 34 and 56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) The abbreviations "PDGF" and "hKGF" render the claims indefinite because abbreviations may not be unique, i.e., they may represent multiple different entities in the art. It is suggested to identify what the abbreviation stands for at least at its first occurrence.

(b) The claims are confusing in the recitation "modified" which is a general term and is not defined in the claims or in the specification. It is unclear, for example, whether "modified" is the property of the entire ligand, such as one digested by restriction endonuclease, or of individual nucleotides. Absent definition, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

(c) The claims are confusing with regard to "modified" RNA ligands because the relationship between "modified' and "relatively higher affinity and specificity" is not recited.

Rejection under 35 U.S.C. 103(a): Obviousness

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 34 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Toole et al. (WO 92/14843) in view of Janjic et al. (5,459,015). The claims are drawn to a method for identifying modified single-stranded RNA ligands to PDGF and hKGF comprising contacting a candidate mixture of modified RNAs with target PDGF or hKGF and partitioning

and amplifying the increased binding affinity RNAs thereby identifying modified RNA ligands to the target. Toole et al. teach essentially the same method (page 38) wherein the ligands are RNA ligands (page 24, lines 24-25), nucleotides in the candidate RNA mixture may be modified by substitution at the 2' or 3' hydroxyl with amine (page 26, line 25) or 2'-fluoro (page 27, line 33) groups and the ligands may be to PDGF or bFGF (Table 1, page 139). The claimed invention method differs from that of Toole et al. wherein the ligands are to hKGF. However, Janjic et al. teach the method of the claimed invention wherein the identified modified RNA ligands comprising 2'-deoxy-2'aminopyrimidines are to bFGF (column 126, claim 5) which is a member of a small family of protein growth factors that includes hKGF (column 6, lines 33-49). The family members share similar properties and were known to have cell transforming activity. Therefore, it would have been obvious to the skilled practitioner in the art at the time the claimed invention was made to identify modified RNA ligands to hKGF by the method of Toole et al. and Janjic et al. because one of ordinary skill in the art would have been motivated by the known utilities of nucleic acid ligands in diagnostic and therapeutic applications as taught by Toole et al. (e.g., pages 17-18 and by Janjic et al. (column 12, lines 61-67).

Conclusion

6. No claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie Zitomer whose telephone number is (703) 308-3985. The examiner can normally be reached on Monday through Friday from 9:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152. The official fax phone number for this Group is (703) 308-4242. The unofficial fax number is (703) 308-8724. The examiner's Rightfax number is 703-746-3148.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196. For questions and requests relating to formal matters contact Patent Analyst Tiffany Tabb at 703-605-1238.

S. Zitomer

Stephanie Zitomer, Ph.D.
April 22, 2002